Effects of complete androgen blockade for 12 and 24 weeks on the pathological stage and resection margin status of prostate cancer

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Aims: To compare the pathological stage and surgical margin status in patients undergoing either immediate radical prostatectomy or 12 and 24 weeks of neoadjuvant hormonal treatment (NHT) in a prospective, randomised study.

Methods: Whole mount sections of 393 radical prostatectomy specimens were evaluated: 128 patients had immediate surgery, 143 were treated for 12 weeks and 122 for 24 weeks with complete androgen blockade.

Results: Histopathology revealed organ confined tumours in 40.4% of patients with clinical stage B disease in the immediate surgery group, whereas 12 and 24 weeks of NHT increased the number of organ confined tumours to 54.6% and 64.8%, respectively. Among patients with clinical stage C tumours, pathological staging found organ confined disease in 10.4%, 31.4%, and 61.2% in the immediate surgery, 12 weeks of NHT, and 24 weeks of NHT groups, respectively. Preoperative NHT caused a significant decrease in positive margins both in patients with clinical stage B and C disease. The extent of margin involvement was not influenced by neoadjuvant treatment.

Conclusions: Neoadjuvant androgenic suppression is effective in reducing both the pathological stage and the positive margin rate in patients with stage B and C prostatic cancer undergoing radical surgery. Some beneficial effects are evident in those patients treated for 24 weeks, and it is reasonable to assume that the optimal duration of NHT is longer than three months.

“...The optimal duration of preoperative androgen suppression has not been determined yet”

Here, we present the final pathological data of a controlled multicentre trial designed to investigate the differences in outcome of radical retroperitoneal prostatectomy in patients with clinically localised prostate cancer treated with immediate surgery or with 12 and 24 weeks of NHT before surgery.

MATERIALS AND METHODS

Trial outlines of the Italian PROSIT study

The PROSIT study (study number 7054IT/0001) is a multicentric, phase III trial comparing immediate radical prostatectomy (RP) with RP after total androgen ablation in patients with surgically resectable clinical stage B or C (T2–T3, N0, M0) prostatic carcinoma. It is an open label, prospective, randomised study assigning patients in a 1:1:1 ratio to one of the following three treatment arms before RP: (1) no hormonal treatment before surgery; (2) “Zoladex” depot 3.5 mg subcutaneously every 28 days plus “Casodex” 50 mg/day orally for 12 weeks (three months); and (3) “Zoladex” depot 3.5 mg subcutaneously every 28 days plus “Casodex” 50 mg/day orally for 24 weeks (six months). “Zoladex” (goserelin acetate; leutinising hormone releasing hormone analogue) and “Casodex” (bicalutamide; antiandrogen) are trademarks of AstraZeneca Ltd.

The primary objective of our study was to evaluate whether NHT with “Casodex” and “Zoladex” for 12 or 24 weeks before RP and bilateral pelvic node dissection in patients with clinical stage B or C increases the time to serum PSA progression.

Abbreviations: NHT, neoadjuvant hormonal treatment; PSA, prostate specific antigen; RP, radical prostatectomy
PSA progression is defined as an increase in PSA concentration of at least 1 ng/ml above the postoperative value (measured at eight weeks) in two subsequent measurements.

The secondary objectives comprise the evaluation of whether NHT influences local tumour stage and resection margin involvement, increases time to clinical progression, and increases overall survival and/or disease specific survival. Clinical progression is defined by the appearance of local relapse and/or one or more distant metastases, as shown by imaging procedures. Full details of the study have been published previously,2,3 and can be obtained from the study coordinators (Professor F Pagano, Padova; Professor A Bono, Varese, Italy).

The data on PSA and disease progression are not yet complete at the time of writing this paper. The present final pathology report deals with two of the secondary objectives—that is, the influence of NHT on local tumour stage and resection margin involvement.

Patients and methods of analysis

Between January 1996 and July 2000, 431 men with prostate cancer were enrolled. Three hundred and ninety three of these 431 patients underwent radical prostatectomy and bilateral pelvic node dissection in the 24 centres participating in the Italian PROSIT study. The differences between the numbers of enrolled men and the numbers of RP specimens, in addition to the small difference in the three treatment arms (see below), result from the fact that 24 of the 431 patients did not undergo surgical treatment, and 14 did not comply with the protocol and therefore were excluded. Whole mount sectioning of the complete RP specimens was adopted in each centre for accurately evaluating the pathological stage of prostate cancer and resection margin status.

The prostatectomy specimens (prostate and seminal vesicles) were covered with India ink and fixed for 48 hours in neutral buffered formalin (4%). After fixation, the distal (apical) portion, the proximal (basal) portion, and the seminal vesicle invasion; pT3b); D1 (metastasis in the regional lymph nodes; pN1). For the purpose of our study B1 and B2 were considered as a single staging category (that is, B).

The presence of cancer at the inked margin of resection in an RP specimen was defined as a positive surgical margin. The extent of a positive margin was classified as focal or extensive. A focal margin was defined as a margin present in only one step section and involving one gland in that section; involvement greater than this was classified as an extensive positive margin. The locations of the positive surgical margins were classified and recorded as apical, prostate body, and prostate base.

By the end of July 2000, the haematoxylin and eosin stained sections of 393 RP specimens were received and evaluated by the reviewing pathologist (RM). The present investigation was based on these 393 cases. Statistical analysis was performed using the χ2 test.

RESULTS

One hundred and twenty eight of the 393 patients were not treated with total androgen ablation before RP was performed, whereas 143 and 122 were treated for 12 and 24 weeks, respectively. Two hundred and ninety eight patients were clinical stage B, whereas 95 were clinical stage C. The three groups were comparable with regard to patient age and serum PSA. In particular, the mean age and range were as follows: untreated group, 65.72 years (range, 52–76); three month androgen ablation, 65.43 years (range, 49–76); six month androgen ablation, 66.16 years (51–76). The median PSA (ng/ml) at the time of enrolment was: untreated group, 10.20; three month androgen ablation, 10.15; six month androgen ablation, 10.0 (table 1).

Morphologically, most of the biopsy specimens from the treated and untreated groups were Gleason score 6 or higher; the percentages at each grade, for all the three groups, were similar. In the untreated group, there was agreement of the Gleason score between the biopsy and surgical specimen in 88 of 128 cases (68.8%); in 39 of the 40 discordant cases there was a downgrading in the biopsy specimen (table 2). The treated tumours with pretreatment cribriform and solid/trabecular

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient and disease characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients [n]</td>
<td>Surgery only</td>
</tr>
<tr>
<td>Mean age in years (range)</td>
<td>65.72 (52–76)</td>
</tr>
<tr>
<td>Clinical stage B [n]</td>
<td>99</td>
</tr>
<tr>
<td>Clinical stage C [n]</td>
<td>29</td>
</tr>
<tr>
<td>PSA (ng/ml) median</td>
<td>10.20</td>
</tr>
<tr>
<td>PSA (ng/ml) range</td>
<td>0.8–763.6</td>
</tr>
</tbody>
</table>

NHT, neoadjuvant hormonal treatment; PSA, prostate specific antigen.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Biopsy versus prostatectomy Gleason grade in untreated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>[2–6]</td>
</tr>
<tr>
<td>2–6</td>
<td>46 (59.7%)</td>
</tr>
<tr>
<td>7</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>8–10</td>
<td>0</td>
</tr>
</tbody>
</table>

Agreement in 88 cases (68.8%), disagreement in 40 (31.2%).
patterns (primary Gleason grade 4 and 5) showed nuclear and cytoplasmic changes, which appeared less pronounced than in the acinar pattern (primary Gleason grade 1 to 3). The hallmark of all the untreated adenocarcinomas was that the tumour nuclei were frequently multinucleolated, the nucleoli being prominent, marginated, and with a perinuclear halo. In the treated cases, the nucleoli became inconspicuous, without being prominent, marginated, and with a perinuclear halo. In tumour nuclei were frequently multinucleolated, the nucleoli were not significant. In both the 12 and 24 weeks of treatment groups, the degree of regression improved as the Gleason score became lower (tables 3 and 4).

Tables 5 and 6 show the results of the evaluation of the pathological stage and resection margin status in the untreated and treated patients with clinical stage B.

After 12 weeks of total androgen ablation there was a higher prevalence of pathological stage B among patients with clinical B tumours, when compared with untreated patients (54.6% in treated patients vs 40.4% in untreated), although the difference was not significant. The percentage of cancers with negative margins was significantly greater in patients treated with 12 weeks of NHT than those treated with immediate surgery only (74.1% vs 53.5%; p = 0.003). Moreover, considering the cancers with positive margins, the percentage of cases with focal involvement was higher in those patients treated for 12 weeks than in untreated ones (53.6% vs 46.0%), although the difference was not significant.

After 24 weeks of treatment, when compared with the immediate surgery group, the proportions of patients with pathological stage B (64.8% vs 40.4%; p = 0.009), negative margins (81.3% vs 53.5%; p < 0.001), and focal involvement of margins (70.6% vs 46.0%; \( \chi^2 \) not significant) were greater and they were also greater than was seen after 12 weeks of treatment (see previous paragraph).

In this group (patients with clinical stage B), NHT did not affect the incidence of seminal vesicle invasion (stage C2) and of involvement of the pelvic lymph nodes (stage D1). Tables 7 and 8 show the results of the pathological evaluation of the whole mount sections in the untreated and treated patients with clinical stage C. For clinical C tumours, the prevalence of pathological stage B and of negative margins in the patients treated for either 12 or 24 weeks was similar to that observed in the clinical B tumours when compared with the untreated group (pathological stage B, 31.4% vs 10.4%; \( p = 0.001 \)). Also in this group, significant pathological downstaging was reached only after 24 weeks of treatment, and there was a significant difference between the longterm and the short-term treatment arms. Negative margins were 65.7% and 64.5% vs 24.1%, respectively (\( p = 0.001 \)). The proportion of cases with focal involvement of the margins was similar in patients treated for 12 and 24 weeks.

### Table 3 Biopsy versus prostatectomy Gleason grade regression after 12 weeks of NHT

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>Prostatectomy</th>
<th>Poor</th>
<th>Good</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–6</td>
<td>9 (9.9%)</td>
<td>40 (44.0%)</td>
<td>42 (46.1%)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>16 (39.0%)</td>
<td>19 (46.3%)</td>
<td>6 (14.7%)</td>
<td></td>
</tr>
<tr>
<td>8–10</td>
<td>6 (54.5%)</td>
<td>5 (45.5%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
</tbody>
</table>

NHT, neoadjuvant hormonal treatment.

### Table 4 Biopsy versus prostatectomy Gleason grade regression after 24 weeks of NHT

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>Prostatectomy</th>
<th>Poor</th>
<th>Good</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–6</td>
<td>6 (7.9%)</td>
<td>26 (34.2%)</td>
<td>44 (57.9%)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>9 (25.7%)</td>
<td>11 (31.4%)</td>
<td>15 (42.9%)</td>
<td></td>
</tr>
<tr>
<td>8–10</td>
<td>5 (45.4%)</td>
<td>42 (36.4%)</td>
<td>2 (18.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Chi square=14.485; p=0.006.
NHT, neoadjuvant hormonal treatment.

### Table 5 Pathological stage in the untreated and treated patients with clinical stage B disease

<table>
<thead>
<tr>
<th>Pathological stage</th>
<th>Surgery only (%)</th>
<th>12 weeks of NHT (%)</th>
<th>24 weeks of NHT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>40 [40.4%]</td>
<td>59 [54.6%]</td>
<td>59 [64.8%]</td>
</tr>
<tr>
<td>C1</td>
<td>45 [45.5%]</td>
<td>33 [30.6%]</td>
<td>23 [25.3%]</td>
</tr>
<tr>
<td>C2</td>
<td>9 [9.1%]</td>
<td>11 [10.2%]</td>
<td>7 [7.7%]</td>
</tr>
<tr>
<td>D1</td>
<td>5 [5.0%]</td>
<td>5 [4.6%]</td>
<td>2 [2.2%]</td>
</tr>
<tr>
<td>Total</td>
<td>99</td>
<td>108</td>
<td>91</td>
</tr>
</tbody>
</table>

Chi square=13.124; p=0.041. Untreated versus 12 weeks of NHT: \( \chi^2=5.311; p=0.199 \) (not significant [NS]). Untreated versus 24 weeks of NHT: \( \chi^2=11.984; p=0.009 \). 12 weeks of NHT versus 24 weeks of NHT: \( \chi^2=2.526; p=0.641 \) (NS).

NHT, neoadjuvant hormonal treatment.

### Table 6 Resection limit status in the untreated and treated patients with clinical stage B disease

<table>
<thead>
<tr>
<th></th>
<th>Surgery only (%)</th>
<th>12 weeks of NHT (%)</th>
<th>24 weeks of NHT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative margins</td>
<td>53 [53.5%]</td>
<td>80 [74.1%]</td>
<td>74 [81.3%]</td>
</tr>
<tr>
<td>Positive margins</td>
<td>46 [46.5%]</td>
<td>28 [25.9%]</td>
<td>17 [18.7%]</td>
</tr>
</tbody>
</table>

Chi square=18.953; p<0.001. Untreated versus 12 weeks of NHT: \( \chi^2=8.613; p=0.009 \). Untreated versus 24 weeks of NHT: \( \chi^2=15.284; p=0.001 \). 12 weeks of NHT versus 24 weeks of NHT: \( \chi^2=1.096; p=0.295 \) (not significant).

NHT, neoadjuvant hormonal treatment.
In addition, for clinical stage C patients NHT did not alter the incidence of seminal vesicle invasion (stage C2), whereas there was a reduced incidence of patients with nodal invasion (stage D1), which was proportional to the duration of treatment.

In most patients prostate cancer originated in the peripheral zone. The most frequent location of the positive resection margins was either in the apex or the body of the prostate.

### DISCUSSION

The morphological evaluation of 393 completely sampled RP specimens shows that NHT before surgery causes relevant cytological and architectural changes. This is in agreement with the information given in Montironi and Schulman’s paper on androgen manipulation and prostate cancer morphology.

The results of the present analyses are also in agreement with the observations made in the study by Srougi et al., where the relation between the biopsy Gleason score and the tissue response to NHT was documented.

There is conflicting evidence regarding pathological downstaging, with some studies suggesting benefit and others no benefit of androgen manipulation before RP (see Montironi and Schulman for a review on this topic). The problem might be related to incomplete sampling of the prostates and the tissue response to NHT was documented.

In addition, for clinical stage C patients NHT did not alter the incidence of seminal vesicle invasion (stage C2), whereas there was a reduced incidence of patients with nodal invasion (stage D1), which was proportional to the duration of treatment.

In most patients prostate cancer originated in the peripheral zone. The most frequent location of the positive resection margins was either in the apex or the body of the prostate.

### Table 7 Pathological stage in the untreated and treated patients with clinical stage C disease

<table>
<thead>
<tr>
<th>Pathological stage</th>
<th>Surgery only (%)</th>
<th>12 weeks of NHT (%)</th>
<th>24 weeks of NHT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>3 (10.4%)</td>
<td>11 (31.4%)</td>
<td>19 (61.2%)</td>
</tr>
<tr>
<td>C1</td>
<td>11 (37.9%)</td>
<td>13 (37.1%)</td>
<td>3 (9.7%)</td>
</tr>
<tr>
<td>C2</td>
<td>5 (17.2%)</td>
<td>5 (14.3%)</td>
<td>6 (19.4%)</td>
</tr>
<tr>
<td>D1</td>
<td>10 (34.5%)</td>
<td>6 (17.2%)</td>
<td>3 (9.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>35</td>
<td>31</td>
</tr>
</tbody>
</table>

Chi square=22.152; p<0.001. Untreated versus 12 weeks of NHT: $\chi^2$=5.221; p=0.207 [not significant (NS)]. Untreated versus 24 weeks of NHT: $\chi^2$=20.024; p<0.001. 12 weeks of NHT versus 24 weeks of NHT: $\chi^2$=9.266; p=0.033 (NS).

NHT, neoadjuvant hormonal treatment.

### Table 8 Resection limit status in the untreated and treated patients with clinical stage C disease

<table>
<thead>
<tr>
<th></th>
<th>Surgery only (%)</th>
<th>12 weeks of NHT (%)</th>
<th>24 weeks of NHT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative margins</td>
<td>7 (24.1%)</td>
<td>23 (65.7%)</td>
<td>20 (64.5%)</td>
</tr>
<tr>
<td>Positive margins</td>
<td>22 (75.9%)</td>
<td>12 (34.3%)</td>
<td>11 (35.5%)</td>
</tr>
</tbody>
</table>

Chi square=13.603; p<0.001. Untreated versus 12 weeks of NHT: $\chi^2$=9.402; p=0.002. Untreated versus 24 weeks of NHT: $\chi^2$=8.306; p=0.004. 12 weeks of NHT versus 24 weeks of NHT: $\chi^2$=0.025; p=0.875 [not significant].

NHT, neoadjuvant hormonal treatment.

A positive surgical margin is defined as the presence of cancer at the inked margin of resection in an RP specimen. It indicates that cancer has not been completely excised. Positive margins may occur even in the absence of evident extracapsular disease. Paulson reported that the status of the surgical margins was the most important prognostic feature in patients treated with RP. The least controversial aspect of neoadjuvant therapy is its impact on surgical margins. Most series, whether prospective and controlled or not, and whatever the type of hormonal deprivation, have shown that neoadjuvant therapy in clinical T2 tumours was associated with a 20–25% decrease in positive margins in RP specimens. As an example, in the Memorial Sloan-Kettering...
Cancer Center study, the percentage of organ confined cancers in patients treated with immediate surgery was 49%, whereas it was 77% in patients given neoadjuvant treatment. In patients with clinical T3 tumours, the effects of neoadjuvant treatment on positive margins are less clear. Although it is generally agreed that NHT has a positive influence on margin status in clinically organ confined tumours (stages T1c–T2 or B), only two randomised studies analysed patients presenting with stage C (T3) prostatic carcinoma. Wijte and colleagues evaluated the effects of three months of administration of Goserelin and Flutamide without documenting a significant decrease of positive margins compared with immediate surgery (59% v 43%; p = 0.14). In a similar study, Van Poppel et al., who gave Estramustine to 55 patients with clinical stage C tumours, found no significant reduction of positive margins (44% v 41.3%).

Our present study confirms the effect of NHT on surgical margin status. For patients with clinical stage B tumours the number of cases with negative surgical margins was significantly greater after 12 and 24 weeks of NHT compared with the immediate surgery group (p < 0.001). The extent of positive margins (focal versus extensive) did not seem to be influenced by androgen suppression, although there was a trend for a higher incidence of focally positive margins in treated patients. NHT also increased the number of cases with negative surgical margins in patients with clinical stage C tumours, when compared with the immediate surgery group (p = 0.001), and no benefit was seen after a longer treatment period. Also in this group, the extent of positive margins was not greatly influenced by androgen suppression.

Our present study is the first randomised series to demonstrate a clear advantage on margin status in stage C tumours as a result of NHT in a population of statistically adequate size. It is also the first to compare immediate surgery with two different durations of androgen suppression, including a sizeable group of patients treated for 24 weeks. The pathological effects of longterm treatment have been investigated in a randomised study by Gleave et al., who compared the effects of three versus eight months of NHT on various clinical and pathological parameters, but a group of controls undergoing immediate surgery was not included. In a population of clinically organ confined tumours (T1c–T2) a significant reduction of positive margins was found for the longer treatment arm (12% v 36%; p = 0.0106). Our present study confirms such findings mainly for stage B tumours following 24 weeks of NHT.

In conclusion, our data show that systemic hormonal treatment is able to “downstage” the primary tumour and decrease the positive margin rate before definitive localised treatment; that is, NHT can kill sufficient numbers of cells so that the tumour has regressed completely, or invovted into the gland. This is in agreement with a much smaller study (40 versus our 393 patients) published by van der Kwast et al., in which the effect on prostate cancer of three versus six months of endocrine treatment was evaluated. The clinical relevance of these advantages has yet to be confirmed because up to now the analysis of time to PSA progression has not revealed significant differences between treatment groups. This is because the follow up period after surgery is still too short—no more than two years.

ACKNOWLEDGEMENTS
This study was supported by a research grant from AstraZeneca Italia S.p.A. Pharmaceuticals.

The following urologists and pathologists participated in the Italian PROSIT study: M Polito, G Muzzonigro, D Minardi, R Montroni (Ancona); F P Selvaggi, S Palazzio, P Bufo (Bari); S Guazzieri, R Bertoldi, C Dogiioni, E Macri (Belluno); A Lembo, L Canclini, D Chiraglia (Bergamo); S Coscioni-Cunico, T Zambolin, M Tanello, R Tardanico (Brescia); E Usai, R Migliari, G Muscas, E Valdes, C Varsi (Cagliari); S Ferretti, P Palladini, C DiGregorio (Carpi); G C Comeri, G Conti, G Lunetta, G Scola (Como); G Signorelli, E Andreotta, R Giordano, E Nisi (Dolo); M Rizzo, R Bartolletti, A Amorosi (Firenze); E Martini, P Andreassi, T Ventura (L’Aquila); W Arribani, R Piazza, C De Gaetani (Modena); D Fontana, R Tarabuzzi, L Gulbetta, E Bollito (Orbassano); F Pagano, T Prayer-Galetti, M Gardiman (Padova); G Fiaccavento, P Belmonte, G Sacchi (Portogruaro); S Rocco Rossetti, C Terrone, G Palestro, D Galliano (Pordenone); G Muto, F Bordari, G S Zappabasso, A M Pisacane (Torino); A Manganeli, G De Robertis, M T De Vecchio (Siena); D Potenzoni, A Gregori, L Serra (San Secondo Parmense); G Anselmo, A Chechin, G A Arrigoni (Treviso); C Selli, C Scott, C A Belrami, F Zattini, P Palazzio (Udine); A V Bono, C Fava, M Salvadore (Varese); A Tasca, A M Negheni, S Meli, A Armani (Vicenza).

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